Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

PATENT Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|---------------------|
| P1 | 6,6-Bis-(4-fluoro-phenyl)- 1-[4-(2-phenylsulfanyl- ethyl)-piperazin-1-yl]- hexan-1-one | S N N F |
| P2 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2-(4- fluoro-phenoxy)-ethyl]- piperazine | F F |
| P3 | 1-{4-[2- (Benzo[1,3]dioxol-5- yloxy)-ethyl]-piperazin-1- yl}-6,6-bis-(4-fluoro- phenyl)-hexan-1-one | H-CI F |
| P4 | l-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(2- phenylsulfanyl-ethyl)- piperazine | s—NNN |
| P5 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2-(4- methoxy-phenoxy)-ethyl]- piperazine | MeO—O N N H—CI H—CI |

App No.: Not Yet Assigned Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

PATENT Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|---|
| Р6 | 1-{4-[2-(2,4-Difluoro- phenoxy)-ethyl]- piperazin-1-yl}-6,6-bis- (4-fluoro-phenyl)-hexan- 1-one | F O F F F F F F F F F F F F F F F F F F |
| P7 | 6,6-Bis-(4-fluoro-phenyl)- 1-[4-(2-phenoxy-ethyl)- piperazin-1-yl]-hexan-1- one | F |
| P8 | 1-{4-[2-(2,4-Dichloro- phenoxy)-ethyl]- piperazin-1-yl}-6,6-bis- (4-fluoro-phenyl)-hexan- 1-one | CI CI F |
| Р9 | 6,6-Bis-(4-fluoro-phenyl)- 1-{4-[2-(4-methoxy- phenoxy)-ethyl]- piperazin-1-yl}-hexan-1- one | MeO—O N N F |
| P10 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(2- phenoxy-ethyl)-piperazine | F F |

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

PATENT Docket 381092000624

| Com- pound | Name | Structure |
|---------------|--|--|
| P11 | 6,6-Bis-(4-fluoro-phenyl)- 1-{4-[2-(3,4,5-trimethoxy-phenoxy)-ethyl]- piperazin-1-yl}-hexan-1- one | MeO O O O O O O O O O O O O O O O O O O |
| P12 | 1-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | F S N N F |
| P13 | [4-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-ethoxy)-2,3,6-trimethyl-phenyl]-carbamic acid tert-butyl ester | H N N N N N N N N N N N N N N N N N N N |
| P14 | 4-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethoxy)-2,3,6-trimethyl-phenylamine | $\begin{array}{c c} & & & \\ & & & \\ & & & \\ H_2N & & \\ & & \\ H-CI & \\ & & \\ H-CI & \\ & & \\ \end{array}$ |
| P15 | 1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-[2-(2,4-dichloro-phenoxy)-ethyl]-piperazine | F CI |

App No.: Not Yet Assigned Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

PATENT Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|---------------------------|
| P16 | [2-(4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-di-tert-butyl-phenoxy)-ethyl]-dimethyl-amine | H-CI H-CI H-CI F |
| P17 | 4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-di-tert-butyl-phenol | F HO H-CI H-CI |
| P18 | 1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | MeO F |
| P19 | 1-[4-(3,5-Di-tert-butyl-4-methoxy-benzyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | MeO F |
| P20 | l-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5-di- tert-butyl-4-methoxy- benzyl)-piperazine | H-CI H-CI |

App No.: Not Yet Assigned Docket No.: 38109.
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

 \mathbf{P} A \mathbf{T} \mathbf{E} \mathbf{N} \mathbf{T} Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|---------------------------------------|
| P21 | {4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-(3,5-di-tert-butyl-4-methoxy-phenyl)-methanone | MeO F |
| P22 | 1-{4-[3,5-Di-tert-butyl-4- (2-dimethylamino- ethoxy)-benzoyl]- piperazin-1-yl}-6,6-bis- (4-fluoro-phenyl)-hexan- 1-one | J J J J J J J J J J J J J J J J J J J |
| P23 | 1-Benzo[1,3]dioxol-5- ylmethyl-4-[6,6-bis-(4- fluoro-phenyl)-hexyl]- piperazine | F H-CI H-CI F |
| P24 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5-di- tert-butyl-benzyl)- piperazine | H-CI H-CI F |
| P25 | {4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-(3,5-di-tert-butyl-4-hydroxy-phenyl)-methanone | HO F |

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|-------------------|
| P26 | 1-[4-(3,5-Di-tert-butyl-4- hydroxy-benzyl)- piperazin-1-yl]-6,6-bis-(4- fluoro-phenyl)-hexan-1- one | HO P |
| P27 | 1-[4-(3,5-Dibromo-4- hydroxy-benzoyl)- piperazin-1-yl]-6,6-bis-(4- fluoro-phenyl)-hexan-1- one | Br N N F |
| P28 | 1-[4-(3,5-Di-tert-butyl-4-hydroxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | F P |
| P29 | 1-[4-(3,5-Di-tert-butyl-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | F |
| P30 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(4-tert- butyl-benzyl)-piperazine | H-CI H-CI F |

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket 381092000624

| Com- pound | Name | Structure |
|---------------|--|---|
| P31 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(9H- thioxanthen-9-yl)- piperazine | S P P P P P P P P P P P P P P P P P P P |
| P32 | 2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-benzothiazole | H-CI H-CI |
| P33 | 6,6-Bis-(4-fluoro-phenyl)- 1-(4-pyrimidin-2-yl- piperazin-1-yl)-hexan-1- one | H-CI F |
| P34 | 2-{4-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-piperazin- 1-yl}-pyrimidine | H-CI H-CI F |
| P35 | 6,6-Bis-(4-fluoro-phenyl)- 1-[4-(9H-thioxanthen-9- yl)-piperazin-1-yl]-hexan- 1-one | S N N N F |

App No.: Not Yet Assigned Docket No.: 38109: Inventor: Terrance P. SNUTCH et al. Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|---|---|
| P36 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,4,5- trimethoxy-benzyl)- piperazine-2-carboxylic acid ethyl ester | MeO N N N N N N N N N N N N N N N N N N N |
| P37 | 6,6-Bis-(4-fluoro-phenyl)- 1-{4-[2-(3,4,5-trimethoxy-benzylamino)-ethyl]- piperazin-1-yl}-hexan-1- one | MeO H N N N N N N N N N N N N N N N N N N |
| P38 | 9,9-Bis-(4-fluoro-phenyl)- 1-[4-(3,4,5-trimethoxy- benzyl)-piperazin-1-yl]- nonan-1-one | H-CI O OMe OMe |
| P39 | (2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethyl)-phenyl-amine | |
| P40 | 1-[9,9-Bis-(4-fluoro- phenyl)-nonyl]-4-(3,4,5- trimethoxy-benzyl)- piperazine | H-CI OMe OMe |

Figure 1

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|---|
| P41 | (4-{4-[Bis-(4-fluoro-phenyl)-methoxy]-butyl}-piperazin-1-yl)-(3,4,5-trimethoxy-phenyl)-methanone | OMe MeO H-CI MeO N N |
| P42 | 6,6-Bis-(4-fluoro-phenyl)- 1-[4-(4-trifluoromethoxy- benzoyl)-piperazin-1-yl]- hexan-2-one | F F N N N N N N N N N N N N N N N N N N |
| P43 | 1-[4-(4-Bromo-benzoyl)- piperazin-1-yl]-6,6-bis-(4- fluoro-phenyl)-hexan-1- one | Br F |
| P44 | 6,6-Bis-(4-fluoro-phenyl)- 5-hydroxy-1-[4-(3,4,5- trimethoxy-benzoyl)- piperazin-1-yl]-hexan-1- one | MeO OH F |
| P45 | 1-{4-[Bis-(4-fluoro- phenyl)-methoxy]-butyl}- 4-(3,4,5-trimethoxy- benzyl)-piperazine | OMe H-CI H-CI MeO N N |

App No.: Not Yet Assigned Docket No.: 381092
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|---|-----------------|
| P46 | 6,6-Bis-(4-fluoro-phenyl)- 6-hydroxy-1-[4-(3,4,5- trimethoxy-benzoyl)- piperazin-1-yl]-hexan-1- one | MeO N N N OH OH |
| P47 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazine-2-carboxylic acid | MeO NeO OH |
| P48 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-(3,4,5-trimethoxy-benzyl)-piperazin-2-one | MeO OMe F |
| P49 | 1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-4-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one | MeO F |
| P50 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,4,5- trimethoxy-benzoyl)- piperazin-2-one | MeO OMe F |

Figure 1

App No.: Not Yet Assigned Docket No.: 381092
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING
BENZHYDRIL SPACED FROM PIPERAZINE

$P\quad A\quad T\quad E\quad N\quad T$ Docket 381092000624

| Com- | | |
|-------|---|---|
| pound | Name | Structure |
| P51 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazin-2-one | MeO OMe |
| P52 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-(3,5-di-tert-butyl-4-methoxy-benzyl)-piperazin-2-one | MeO F |
| P53 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-[2-(4-fluoro-phenoxy)-ethyl]-piperazin-2-one | F O O O O O O O O O O O O O O O O O O O |
| P54 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5-di- tert-butyl-4-methoxy- benzoyl)-piperazin-2-one | MeO F |
| P55 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one | MeO F |

Figure 1

App No.: Not Yet Assigned Docket No.: 381093
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING
BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|--|---|
| P56 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5-di- tert-butyl-4-methoxy- benzyl)-piperazin-2-one | N N N N N N N N N N N N N N N N N N N |
| P57 | 1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-4-(3,5-di-tert-butyl-4-hydroxy-benzoyl)-piperazin-2-one | F N N N N N N N F |
| P58 | 6,6-Bis-(4-fluoro-phenyl)- 1-[4-(3,4,5-trimethoxy- benzoyl)-piperazin-1-yl]- hex-5-en-1-one | F F |
| P59 | 1-{4-[2-(3,4-Dimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | F F |
| P60 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2-(3,4- dimethoxy-phenoxy)- ethyl]-piperazine | F F |

Figure 1

App No.: Not Yet Assigned Inventor: Terrance P. SNUTCH et al. Docket No.: 381092000624

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|--|----------------------------------|
| P61 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4- (3,4,5-trimethoxy- benzyl)-piperazine-2- carboxylic acid | OMe OMe OMe OMe CO2H |
| P62 | 4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1- (3,4,5-trimethoxy-benzyl)-piperazine-2-carboxylic acid ethylester | OMe OMe OMe |
| P63 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,4- dimethoxy-benzyl)- piperazine | OMe OMe |
| P64 | 1-[4-(3,4-Dimethoxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | OMe OME F |
| P65 | 1-[2- (Benzo[1,3]dioxol-5- yloxy)-ethyl]-4-[6,6- bis-(4-fluoro-phenyl)- hexyl]-piperazine | |

Figure 1

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|--|
| P66 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2- (3,4,5-trimethoxy- phenoxy)-ethyl]- piperazine | OMe OMe OMe |
| P67 | 1-(4-Amino-2,3,5- trimethyl-phenoxy)-3- {4-[6,6-bis-(4-fluoro- phenyl)-hexyl]- piperazin-1-yl}- propan-2-ol | OH N N F |
| P68 | 1-{4-[3-(4-Amino- 2,3,5-trimethyl- phenoxy)-2-hydroxy- propyl]-piperazin-1- yl}-6,6-bis-(4-fluoro- phenyl)-hexan-1-one | H _N |
| P69 | 1-(4-Benzothiazol-2- yl-piperazin-1-yl)-6,6- bis-(4-fluoro-phenyl)- hexan-1-one | N N N N N N N N N N N N N N N N N N N |
| P70 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(3,5- bis-trifluoromethyl- benzyl)-piperazine | F F F F F F F F F F F F F F F F F F F |

App No.: Not Yet Assigned Docket No.: 381092
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING
BENZHYDRIL SPACED FROM PIPERAZINE

| Co | | |
|---------------|--|---|
| Com- pound | Name | Structure |
| P71 | 1-[4-(3,5-Bis- trifluoromethyl- benzoyl)-piperazin-1- yl]-6,6-bis-(4-fluoro- phenyl)-hexan-1-one | F F F F F F F F F F F F F F F F F F F |
| P72 | 1-[4-(4-tert-Butyl- benzoyl)-piperazin-1- yl]-6,6-bis-(4-fluoro- phenyl)-hexan-1-one | N N F |
| P73 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(4- bromo-benzyl)- piperazine | Br N N |
| P74 | 2-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethylsulfanyl)-benzothiazole | S S S S S S S S S S S S S S S S S S S |
| P75 | 6,6-Bis-(4-fluoro- phenyl)-1-[4-(4- hydroxy-3,5- dimethoxy-benzoyl)- piperazin-1-yl]-hexan- 1-one | OMe N N N N N N N N N N N N N N N N N N N |

Figure 1

App No.: Not Yet Assigned Docket No.: 38109: Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|---|---|
| P76 | 4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-dibromo-phenol | Br N N F |
| P77 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-(4- trifluoromethoxy- benzyl)-piperazine | F F N N N F |
| P78 | (2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethyl)-(3,4,5-trimethoxy-benzyl)-amine | OMe H N N N N N N N N N N N N N N N N N N |
| P79 | 1-{4-[2-(4-Fluoro- phenoxy)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one | F F |
| P80 | 6,6-Bis-(4-fluoro- phenyl)-1-[4-(2- phenylamino-ethyl)- piperazin-1-yl]-hexan- 1-one | O N N N N N N N N N N N N N N N N N N N |

Figure 1

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket <u>381092000624</u>

| Com- pound | Name | Structure |
|---------------|---|---|
| P81 | 1-[6,6-Bis-(4-fluoro- phenyl)-hexyl]-4-[2- (2,4-difluoro- phenoxy)-ethyl]- piperazine | F C F F F F F F F F F F F F F F F F F F |
| P82 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-benzamide | |
| P83 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-chlorobenzamide | |
| P84 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-methyl-benzamide | OH ₃ |
| P85 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-4-isopropylbenzamide | |

Figure 1

App No.: Not Yet Assigned Docket No.: 381092
Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING
BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|--|-----------|
| P86 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-4-tert-butylbenzamide | |
| P87 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-fluoro-benzamide | F F |
| P88 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-benzamide | |
| P89 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-chloro-benzamide | |

Figure 1

App No.: Not Yet Assigned Docket No.: 38109: Inventor: Terrance P. SNUTCH et al. Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|--|-----------------|
| P90 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-methyl-benzamide | CH ₃ |
| P91 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-isopropyl-benzamide | |
| P92 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-tert-butyl-benzamide | |
| P93 | N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-fluoro-benzamide | F F |

Figure 1

App No.: Not Yet Assigned Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

| Com- pound | Name | Structure |
|---------------|--|-----------|
| P94 | 1-[4-(2-Benzylamino- ethyl)-piperazin-1-yl]- 6,6-bis-(4-fluoro- phenyl)-hexan-1-one | |
| P95 | 1-{4-[2-(4-Chloro- benzylamino)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one | |
| P96 | 6,6-Bis-(4-fluoro- phenyl)-1-{4-[2-(4- methyl-benzylamino)- ethyl]-piperazin-1-yl}- hexan-1-one | |
| P97 | 6,6-Bis-(4-fluoro- phenyl)-1-{4-[2-(4- isopropyl- benzylamino)-ethyl]- piperazin-1-yl}-hexan- 1-one | |

Figure 1

Inventor: Terrance P. SNUTCH et al.
Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

PATENT Docket 381092000624

| Com- pound | Name | Structure |
|---------------|---|---------------|
| P98 | 1-{4-[2-(4-tert-Butyl-benzylamino)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | |
| P99 | 1-{4-[2-(4-Fluoro- benzylamino)-ethyl]- piperazin-1-yl}-6,6- bis-(4-fluoro-phenyl)- hexan-1-one | |
| P100 | 6,6-Bis-(4-fluoro- phenyl)-1-[4-(1- hydroxy-pyridine-4- carbonyl)-piperazin-1- yl]-hexan-1-one | HO N |
| P101 | 4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-dimethoxy-phenol | OMe HO OMe |

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING
BENZHYDRIL SPACED FROM PIPERAZINE

$P\quad A\quad T\quad E\quad N\quad T$ Docket 381092000624

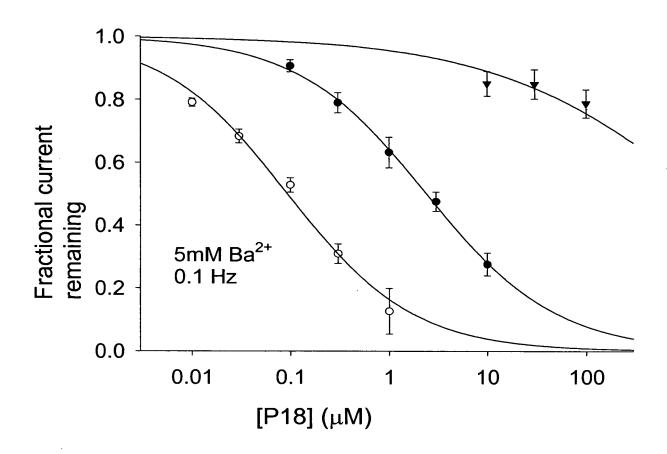
| Com- pound | Name | Structure |
|---------------|--|---|
| P102 | 9,9-Diphenyl-1-[4- (3,4,5-trimethoxy- benzyl)-piperazin-1- yl]-nonan-1-one | OMe OMe OMe OMe |
| P103 | 1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-2-methyl-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | OMe P |
| P104 | 1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-3-methyl-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | OMe N N N |
| P105 | 1-[4-(3,5-Di-tert-butyl-benzoyl)-2-methyl-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one | F N N N N N N N N N N N N N N N N N N N |
| P106 | 1-[4-(4-tert-Butyl- benzoyl)-2-methyl- piperazin-1-yl]-6,6- bis-(4-fluoro-phenyl)- hexan-1-one | F N N N N N N N N N N N N N N N N N N N |

Inventor: Terrance P. SNUTCH et al.

Title: CALCIUM CHANNEL INHIBITORS COMPRISING BENZHYDRIL SPACED FROM PIPERAZINE

P A T E N T Docket 381092000624

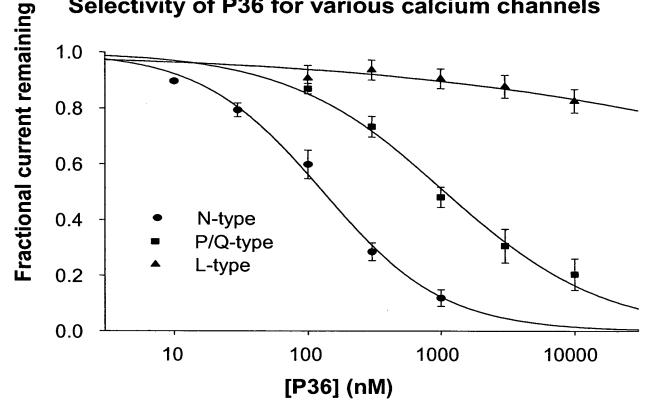
Selectivity of P18 for various calcium channels



- \circ N-type IC₅₀ = 0.11 ± 0.02 μ M (n=5)
- P/Q-type IC₅₀ = $2.71 \pm 0.28 \mu M$ (n=5)
- ▼ L-type IC₅₀ >> 100 μM (n=5)

PATENT Docket 381092000624

Selectivity of P36 for various calcium channels



N-type IC50 =
$$136 \pm 13$$
 nM (n=6)

$$P/Q$$
-type $IC50 = 920 \pm 123 \text{ nM} \text{ (n=5)}$

L-type IC50 >>> 10
$$\mu$$
M (n=5)

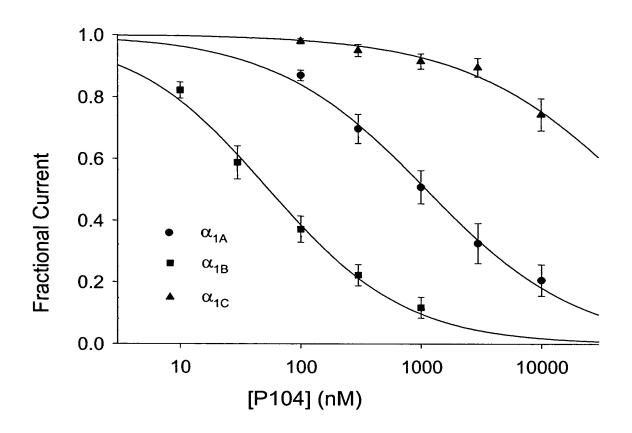
Inventor: Terrance P. SNUTCH et al.

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Effect of P104 on Various HVA Ca2+ Channels



P/Q-type $IC_{50} = 1659 \pm 811$ nM (n=5)

N-type $IC_{50} = 61 \pm 11 \text{ nM (n=5)}$

L-type $IC_{50} >> 10 \mu M$ (n=5) (estimate : 144 μM)